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ESSAY

Neutropenic Fever of Undetermined Origin (N-FUO): Why Not Use the Naproxen Test?

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Neutropenic fever of undetermined origin (N-FUO) following intensive chemotherapy is one of the most challenging problems for the physician because of the seriousness and urgent need for intervention. All neutropenic febrile patients with a granulocyte count less than 500/μl require immediate hospitalization since this is often caused by life-threatening infections, such as septicemia, abscess, and pneumonia. Upon admission to the hospital, an appropriate investigation, including history, physical examination, microbiological examinations such as smears or cultures of sputum, blood, urine, stool, and discharge from local lesions, radiological examinations such as chest roentgenogram, and computed tomographic scans of the abdomen and pelvis, should be performed. Then an appropriate empirical antibiotic regimen should be initiated as soon as possible (1,2).

Unfortunately, not all patients with febrile neutropenia respond to carefully selected empirical antibiotic regimens, nor do they always show evidence of infection to explain the fever even after extensive studies (3–5). In those patients who fail to show any evidence of infection and to respond to an adequate antibiotic therapy, the diagnosis of N-FUO is established. Following chemotherapy, in neutropenic patients, about 60% of fevers are caused by infection (1), and approximately 30% of the infected patients have culture-proven bacteremia. Another 20% of these patients can be established to have fever of bacterial etiology without bacteremia, and in less than 10% of the patients, infection is caused by nonbacterial causes, such as viruses, fungi, and parasites. The remaining febrile neutropenic patients seem to have noninfectious etiology of fever. Accordingly, many neutropenic febrile patients continue to have persistent fever despite well-selected empirical antibiotic regimens (3,6). Obviously, these antibiotic-nonresponsive patients who are negative for microbiological studies cause a great dilemma for the physician. In fact, in some studies, antibiotic therapy has been able to be discontinued with most of these patients experiencing no harmful effects even though sometimes they have continued to have a persistent fever (3,4). In these patients, neoplastic fever is a real possibility (1,7).

In the absence of bacterial infection in patients with

fever, unrestrained use of multiple antibiotics for a prolonged period, especially in the immunocompromised neutropenic patient, is unwise and dangerous. It may not only be detrimental to the patient due to the high risk of developing superinfections, with resistant bacterias and fungi, but also could expose the patient to the unnecessary danger of other side effects of antibiotics, such as nephrotoxicity, coagulopathy, and hepatotoxicity, as well as certain allergic reactions. Furthermore, there are the additional expenses of medical care arising from the use of expensive antibiotics and prolonged hospitalization during antibiotic treatment and investigation. The assumption that there may be an infection, which is yet unidentified, compels the physician to perform repetitive expensive laboratory and radiological tests.

There is no ideal management for N-FUO. In the past 10 years or more, there have been extensive trials of various antibiotic regimens, including broad-spectrum monotherapies and combinations of several antibiotics based on spectrum of coverage of antibiotics on various microorganisms. Most of these studies have found no clinically discernible difference in clinical response between one antibiotic regimen versus another and also monotherapy versus multiple-antibiotic regimens (8–12). This may be explained, at least in part, by the hypothesis that many cases of N-FUO are not caused by infection. According to our experience with the *naproxen test* and long-term follow-up evaluation of patients with N-FUO, most patients with N-FUO eventually have been proven to have neoplastic fever (1,4,6,7).

Our recently proposed approach with the naproxen test seems to offer a reasonable and safe solution for patients with N-FUO with minimal discomfort for the patient and a considerable saving of medical care cost. The naproxen test, given to the patient with N-FUO after failure of clinical response with an appropriate empirical antibiotic regimen, consists of oral administration of three doses of naproxen (375 mg) at 12-hr intervals. If interruption of antibiotic treatment is considered detrimental to the patient, the challenge of the drug can be done concurrently with administration of antibiotics. The patient showing complete defervescence and sustained normal temperature while receiving naproxen is most likely to have neoplastic fever. In our series, a total of 21 patients with the diagnosis of N-FUO, including 17 patients previously published (4,6,13), were subjected for analysis of the naproxen test. Fifteen patients had acute nonlymphocytic leukemia and 6 had other neoplastic diseases. Complete defervescence occurred in 13 patients. Eventually all of them were found to have neoplastic fever. No defervescence occurred in 7 patients. Among these patients, 6 were found to have definitely proven infections. The remaining 1 patient had no obvious infection but had extensive necrotic tumors. Incomplete defervescence with partial lysis of fever occurred in 1 patient, who, in final analysis, was diagnosed to have neoplastic fever. In another reported series, 12 N-FUO pediatric patients were treated with naproxen. Ten patients showed complete lysis of fever and all were found to have neoplastic fever. Two patients did not respond to naproxen and proved to have culture-positive infections (14).

In continuous follow-up evaluation of naproxen-responded patients with N-FUO, almost all were proved not to have any infection, including bacterial, viral, fungal, and parasitic infection. On the other hand, if the naproxen test failed to result in complete defervescence, more than 95% of these patients eventually were found to have an infection, usually a hidden or masked serious infection (1,4,6,7,14). Accordingly, we believe there is no reason to continue on empirical antibiotic therapy for those patients with N-FUO who respond to the naproxen test with complete and sustained lysis of fever while on the drug.

Considering this observation and experience, it is reasonable and safe to initiate the naproxen test when the patient who is diagnosed as having N-FUO does not show any significant defervescence and clinical improvement after appropriate empirical antibacterial therapy for more than 7 days. The naproxen test used at this stage may obviate the need for the empirical addition of antiviral, antifungal, or broader-spectrum antibacterial therapy. Even though the patient continues to have a persistent neutropenia, if there is a response to the naproxen test with defervescence, the patient's clinical condition would rapidly improve, and it may become clear that the patient would not require any further aggressive antibiotic therapy. Usually there is no relapse of fever after 1 or 2 weeks' treatment with naproxen, and by then granulocytopenia often improves. However, should complete lysis of fever not occur with the naproxen test, presence of an occult infectious process should be seriously considered, and it makes a strong case to continue the patient on antibiotic therapy, even add antifungal therapy, and proceed for further diagnostic investigation.

It is imperative for the physician to understand the serious nature of N-FUO, and the etiology of fever should be pursued carefully with an application of intellectual exercise. However, the physician should not be deterred from using the naproxen test since it often shortens the suffering of the patient and assists in determining the right direction for management of febrile neutropenia.

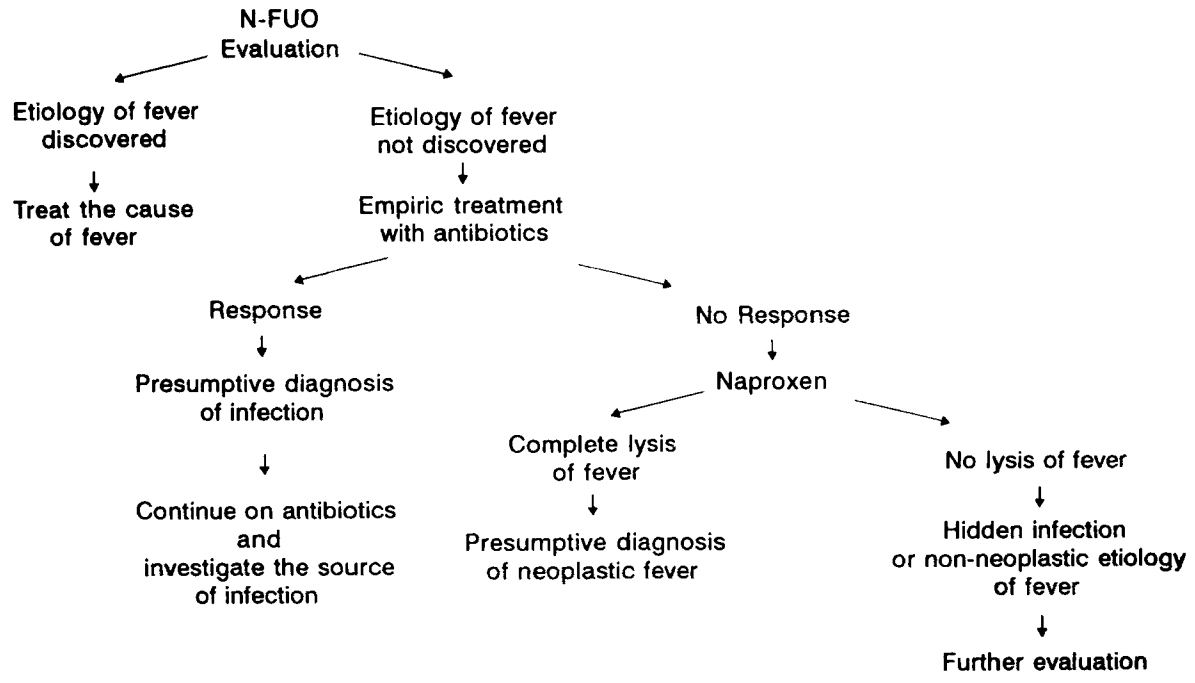

Figure 1. Decision tree illustrating a proposed guideline for the management of a N-FUO patient with cancer. Note that the naproxen test is used in differentiating between neoplastic and nonneoplastic etiology of antibiotic-unresponsive fever.

For safety of the patient and economy of medical care cost, we would propose the decision tree shown in Figure 1. This approach will solve the problem of N-FUO in the majority of cases. Then, why not use the naproxen test for N-FUO?

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